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Childhood trauma- and cannabis-associated microstructural white matter changes in patients with psychotic disorder: a longitudinal family-based diffusion imaging study

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Abstract

Background. Decreased white matter (WM) integrity in patients with psychotic disorder has been a consistent finding in diffusion tensor imaging (DTI) studies. However, the contribution of environmental risk factors to these WM alterations is rarely investigated. The current study examines whether individuals with (increased risk for) psychotic disorder will show increased WM integrity change over time with increasing levels of childhood trauma and cannabis exposure.

Methods. DTI scans were obtained from 85 patients with a psychotic disorder, 93 non-psychotic siblings and 80 healthy controls, of which 60% were rescanned 3 years later. In a whole-brain voxel-based analysis, associations between change in fractional anisotropy (Δ FA) and environmental exposures as well as interactions between group and environmental exposure in the model of FA and Δ FA were investigated. Analyses were adjusted for *a priori* hypothesized confounding variables: age, sex, and level of education.

Results. At baseline, no significant associations were found between FA and both environmental risk factors. At follow-up as well as over a 3-year interval, significant interactions between group and, respectively, cannabis exposure and childhood trauma exposure in the model of FA and Δ FA were found. Patients showed more FA decrease over time compared with both controls and siblings when exposed to higher levels of cannabis or childhood trauma.

Conclusions. Higher levels of cannabis or childhood trauma may compromise connectivity over the course of the illness in patients, but not in individuals at low or higher than average genetic risk for psychotic disorder, suggesting interactions between the environment and illness-related factors.

Introduction

Reduced fractional anisotropy (FA), widely reported in patients with psychotic disorder (Ellison-Wright and Bullmore, 2009), but not in individuals at higher than average genetic risk (siblings of patients) may reflect disease-related dysconnectivity or disease-related differential sensitivity to the environment (Boos *et al.*, 2013; Domen *et al.*, 2013). The risk for psychosis, a condition with adolescent onset, has been related to environmental exposures such as pre- or postnatal birth complications, cannabis use, childhood trauma (Varese *et al.*, 2012; Misiak *et al.*, 2017), and growing up in an urban environment (van Os and Kapur, 2009). These environmental stressors may be the trigger (Cornblatt *et al.*, 2003) or the 'second hit' (Maynard *et al.*, 2001), contributing to the emergence of a psychotic illness. However, the potential impact of these environmental risks on white matter (WM) connectivity (Andreasen *et al.*, 1998; Friston, 1998) has not been the subject of detailed investigation in patients with a psychotic disorder. Cross-sectional studies did explore genetic factors, showing a moderate-to-high heritability of WM FA, ranging from 0.4 to 0.7 (Voineskos, 2015). Also, several candidate genes for WM heritability have been proposed, such as neuregulin1-tyrosine kinase receptor ErbB4, involved in oligodendrocyte, myelin, and axonal development and maintenance (Wang *et al.*, 2009). Various hypotheses have been postulated, associating environmental risk factors with WM alterations. Cannabis use may induce apoptosis of oligodendrocyte progenitors, affecting WM development (Molina-Holgado *et al.*, 2002). In the

literature to date, there is evidence to suggest a negative association between cannabis use and WM volume in patients with schizophrenia (Cahn *et al.*, 2004; Szeszko *et al.*, 2007). Results from diffusion tensor imaging (DTI) studies are less clear and have shown increased as well as decreased FA in cannabis-using v. non-using patients with schizophrenia (Peters *et al.*, 2010; James *et al.*, 2011). The same ambiguity is seen in samples of non-psychotic substance users compared with non-users, which, on the one hand, showed microstructural WM alterations in specific pathways (corpus callosum and superior longitudinal fasciculus) (Baker *et al.*, 2013) and the hippocampus (fimbriae), corpus callosum (splenium), commissural fibers (Zalesky *et al.*, 2012), as well as, on the other hand, absence of FA differences (Arnone *et al.*, 2008).

Studies on early-life stress in otherwise healthy children have shown associations between cortisol reactivity and possible alterations in hippocampal and amygdala volumes (Pagliaccio *et al.*, 2014). Corticosteroids may suppress the final mitosis of glial cells necessary for myelination, influencing WM microstructure (Teicher *et al.*, 2002). This model is supported by studies showing reduced corpus callosum volume in paediatric inpatients with a history of abuse and neglect (Teicher *et al.*, 2004) and reduced FA in the left inferior longitudinal fasciculus (ILF) in young adults witnessing domestic violence in childhood (Choi *et al.*, 2012). To date, longitudinal diffusion weighted imaging studies of patients with schizophrenia are scarce (Canu *et al.*, 2015) and apart from studies investigating the effect of medication on WM diffusion measures (Ozcelik-Eroglu *et al.*, 2014; Reis Marques *et al.*, 2014), no study has examined whether traumatic experience has a differential effect on FA over time in individuals with or without (liability for) psychotic disorder (Bendall *et al.*, 2008).

In a cross-sectional analysis of the baseline DTI scans of the current sample, patient-specific microstructural WM alterations were found (Domen *et al.*, 2013). These alterations remained relatively stable over a 3-year time course in contrast to a decline in mean FA in the non-affected siblings compared with healthy controls (Domen *et al.*, 2017). Consequently, both patients and siblings had decreased FA with respect to controls at follow-up. The aim of the current investigation was to study whether microstructural alterations over time were conditional on the exposure on two of the most examined environmental risk factors for schizophrenia; cannabis use and childhood trauma, for which biological plausibility exists. More specifically, we hypothesized that individuals at increased genetic risk (patients and siblings) with higher levels of exposure to these environmental risk factors would show reduced WM FA over time.

Methods

Participants

Subjects were recruited in the context of a multicenter longitudinal study (Genetic Risk and Outcome of Psychosis, G.R.O.U.P.) in the Netherlands (Korver *et al.*, 2012). At baseline, 300 participants were included of which 258 underwent a DTI scan. At follow-up, approximately 3 years later (mean: 3.3 years), DTI scans were acquired from a sample of 180 participants, of which 159 provided a valid pair of DTI scans for the longitudinal analysis (see Domen *et al.* (2013, 2017) and the Supplementary Method section for further information on inclusion and exclusion criteria, family composition and diagnostic assessments (Domen *et al.*, 2013, 2017).

The standing ethics committee approved the study protocol, and all participants gave written informed consent in accordance with the committee's guidelines.

Measures

Level of psychotic symptomatology at the time of scanning was assessed with the Positive and Negative Symptom Scale (PANSS) (Kay *et al.*, 1987).

Educational level was defined as highest accomplished level of education. Handedness was assessed using the Annett Handedness Scale (Annett, 1970).

Antipsychotic medication

The determination of (lifetime) antipsychotic (AP) medication use at baseline and cumulative AP exposure during the 3-year follow-up period has been described in the online Supplementary Method section based on Domen *et al.* (2013, 2017).

Substance use

Substance use was measured at both time points with the Composite International Diagnostic Interview (CIDI) sections B-J-L (WHO, 1990). As data of drug use over the last 3 years were not available, cannabis and other drug exposure was assessed as reported frequency of use during the last 12 months and lifetime use (mean number of times until baseline measurement). CIDI frequency data on alcohol (weekly consumptions), lifetime cannabis, and other drug use was available at follow-up for, respectively, 158 participants (1% missing data), 155 participants (3% missing data), and 157 participants (1% missing data). Despite the fact that the association between alcohol or other drugs and psychosis risk has been studied less than cannabis and provided a less clear picture, these substances may well contribute to some of the WM variation (Nesvåg *et al.*, 2007; Willi *et al.*, 2017), and were therefore considered potential confounders (see Statistical analyses).

Childhood trauma: Childhood trauma was assessed at baseline with the Dutch version of the Childhood Trauma Questionnaire Short Form (CTQ) (Thombs *et al.*, 2009). The short CTQ consists of 25 items rated on a five-point Likert scale (1 = never true to 5 = very often true) inquiring about traumatic experiences in childhood. Five types of childhood maltreatment were assessed: emotional, physical and sexual abuse, and emotional and physical neglect, with five questions covering each type of trauma (Bernstein *et al.*, 1997). The mean of these 25 items (range 5.0–25.0) created a general measure of childhood trauma. The CTQ data were missing for one patient.

Image acquisition

Magnetic resonance imaging scans were obtained at Maastricht University, the Netherlands, using an Allegra Magnetom MR (Siemens, Erlangen, Germany) operating at 3.0 Tesla. At both measurement points, microstructural anatomy was examined using DTI with an echo-planar-imaging sequence (field of view 230 mm × 230 mm, TR 10800 ms, TE 84 ms, voxel size 1.8 mm × 1.8 mm × 1.8 mm, *b*-value 1000 s/mm², 85 slices, no overlap). As a result of an update of the scanner software during baseline acquisition, two DTI sequences were used: one with 76 directions [of which four T2-weighted (B0) and 72 diffusion-

weighted (B1000)] and one with 81 directions ($8 \times B0$ and $73 \times B1000$). Gradient directions were identical in both sequences. A potential association between the proportion of baseline scans and group was investigated using a Pearson χ^2 test.

At follow-up, the DTI sequence comprised 81 directions ($8 \times B0$ and $73 \times B1000$). Total acquisition time of the DTI sequence was 15 min.

DTI analysis

Processing of DTI data was performed using tract-based spatial statistics (TBSS) v1.2 in FSL 4.1.6 (FMRIB Analysis Group, Oxford, UK, <http://www.fmrib.ox.ac.uk/analysis/research/tbss>). The consecutive processing steps are described in the online Supplementary Method section (based on Domen *et al.*, 2013, 2017). For the current study, three mean FA skeletons were created; for the cross-sectional analysis at baseline ($n = 258$: controls, siblings, patients) and at follow-up ($n = 180$), and for the longitudinal analysis ($n = 159$), one based on six groups (3 groups \times 2 time points).

Statistical analyses

In order to use a multilevel (mixed-effects) model and to be able to calculate a mean FA 'change' (mean FA at baseline minus mean FA at follow-up) for the longitudinal model, which was not compatible with the standard protocol in TBSS, data were analyzed in R (version 3.2.0), a free software environment for statistical computing and graphics (Team, 2015). From the 38 labeled WM tracts, skeleton mean FA values per participant per time point were extracted and exported to R. Since the mean FA values per subject were based on varying number of voxels, depending on the region, we used a model in which the error variance for a particular observation was inversely weighted by the number of voxels within the corresponding region.

Cross-sectional analysis at baseline and follow-up

As of the three-level grouping structure of the data, compromising statistical independence of the observations, a multilevel (mixed-effects) model was fitted. FA was the dependent variable, group (dummy variables with the controls as the reference category, controls = 0, siblings = 1, patients = 2), and the environmental exposures (lifetime and last year cannabis exposure, childhood trauma exposure) were the independent variables and random effects (intercepts) were added for both subject and family.

The statistical basic model was: $FA = \beta_0 + \beta_1 (\text{group}) + \beta_2 (\text{environmental exposure}) + \beta_3 (\text{group} \times \text{environmental exposure})$. This model included the *a priori* hypothesized confounding variables age, sex, and level of education as fixed effects. In case of significant findings, additional covariates [i.e. alcohol consumption, lifetime other drug use, and body mass index (BMI)] were separately added to the model.

Main effects of the environmental exposures (controlled for group), as well as group \times environmental exposures interactions in the model of FA were examined. The environmental exposures were entered both as linear and as factored variables (i.e. representing the distribution of scores divided by its tertiles: lifetime cannabis use: no, moderate, or heavy cannabis use; childhood trauma exposure: low, moderate, or high trauma exposure), allowing visualization of dose-response. In case of significant

interaction effects, stratified analyses were conducted in order to quantify whether the association between environmental exposure and FA differed between the three groups.

To examine whether childhood trauma and lifetime cannabis use contributed independent effects, planned sensitivity analyses were performed with both environmental exposures in the model.

To examine whether the scanner software update at baseline affected the results, the interaction analyses at baseline were repeated in subgroups stratified by the number of scan directions: 76 ($n = 191$) v. 81 ($n = 67$) directions.

Longitudinal analysis

A mean FA 'change' (delta, Δ) per participant per region ($n = 159$) was calculated by subtracting mean FA at baseline from mean FA at follow-up. The same analyses were carried out as described in the cross-sectional part, now using Δ FA as the dependent variable and group and the environmental exposures (lifetime and last year cannabis exposure, childhood trauma exposure) as the independent variables.

In addition, to control for a potential effect of depression on Δ FA, the main longitudinal analysis was repeated with exclusion of the subgroup of participants in the control ($n = 11$) and sibling group ($n = 15$) with a history of a depressive disorder.

Since our previous study showed a small effect of last 3-year and lifetime AP use on Δ FA (Domen *et al.*, 2017), planned sensitivity analyses were performed to rule out potential AP effects, using patient subgroups [with low, moderate, and high AP exposure (for the number of participants per subgroup see online Supplementary Table)]. Thus, the group \times environmental exposure interactions in the model of Δ FA were examined in three AP subgroups to ascertain whether a potential effect remained significant in the respective subgroups.

Results

Demographics

The patients represented a relatively stable population (not in need of inpatient care or intensive treatment), as reflected by the low PANSS scores and the number of patients that fulfilled the remission criteria (Table 1). The gender distribution in the samples was skewed, showing more male patients and male siblings as heavy cannabis users and more male patients and female controls exposed to high levels of childhood trauma at follow-up (Table 2). The mean current dosage of AP medication in terms of standard haloperidol equivalents was 5.5 milligrams (mg) (S.D. = 4.6) at baseline and 4.7 mg (S.D. = 5.1) at follow-up (over the last 3 years). The proportion of baseline scans with 76 directions did not differ between the groups (84% in controls, 82% in siblings, and 71% in patients: $\chi^2 = 3.02$, $df = 2$, $p = 0.22$).

Cross-sectional analysis of FA and environmental risk factors at baseline

There were no significant associations between cannabis exposure and FA (lifetime: $B = 0.002$, $p = 0.24$, last year: $B = 1.0 \times 10^{-5}$, $p = 0.43$) or between childhood trauma exposure and FA ($B = -0.001$, $p = 0.60$). In addition, no significant interactions were found between cannabis exposure and group in the model of FA (lifetime: $\chi^2 = 1.3$, $df = 2$, $p = 0.52$, last year: $\chi^2 = 0.1$, $df = 2$, $p = 0.93$) and between childhood trauma and group in the model of FA

Table 1. Demographic characteristics of the participants [baseline ($n = 258$) and longitudinal analysis ($n = 159$)]

Time point	Controls		Siblings		Patients	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Number	80	49	93	55	85	55
Scan interval (days)	1222 \pm 198		1177 \pm 101		1196 \pm 121	
Age at scan (years)	30.8 \pm 10.8	34.4 \pm 10.9	29.4 \pm 8.8	34.1 \pm 8.5	28.3 \pm 7.0	32.0 \pm 6.2
Sex male (%)	29 (36%)	19 (39%)	49 (53%)	29 (53%)	58 (68%)	40 (73%)
Handedness ^a	76.3	83.2	73.9	78.0	72.8	72.2
Level of education ^b	5.4 \pm 1.8	5.4 \pm 2.0	5.1 \pm 2.1	5.4 \pm 2.1	4.1 \pm 2.0	4.5 \pm 1.9
Body mass index	23.3 \pm 3.2	24.3 \pm 3.7	23.3 \pm 3.3	24.2 \pm 3.9	24.5 \pm 4.2	25.9 \pm 4.8
Age of onset (years)	–		–		22.8 \pm 6.4	21.8 \pm 6.3
Illness duration (years)	–		–		5.4 \pm 3.6	10.3 \pm 4.0
Antipsychotics	–		–		6693 \pm 6254 ^c	5335 \pm 5715 ^d
Diagnosis						
Schizophrenia	–		–		59	33
Schizoaffective dis.	–		–		9	16
Schizophreniform dis.	–		–		4	–
Psychotic dis. NOS	–		–		11	6
Brief psychotic episode	–		–		2	–
Major depressive disorder ^e	12	11	18	15	–	
Substance use						
Cannabis	7.8 \pm 21.9 ^f	4.8 \pm 32.0 ^g	19.3 \pm 37.2 ^f	7.1 \pm 49.1 ^g	44.0 \pm 47.0 ^f	36.5 \pm 105 ^g
Other drugs	0.90 \pm 4.7 ^f	0.0	6.2 \pm 31.4 ^f	0.0	42.4 \pm 90.8 ^f	15.2 \pm 57.0 ^g
Alcohol	5.0 \pm 7.0 ^h	6.3 \pm 10.8 ⁱ	9.8 \pm 17.3 ^h	6.0 \pm 5.4 ⁱ	5.0 \pm 9.1 ^h	4.9 \pm 7.6 ⁱ
Trauma score	6.7 \pm 1.8	6.6 \pm 1.5	6.8 \pm 1.5	6.6 \pm 1.2	8.0 \pm 2.5	7.5 \pm 2.0
PANSS						
Positive symptoms	7.3 \pm 1.1	7.4 \pm 0.8	7.3 \pm 0.9	7.4 \pm 0.7	10.4 \pm 5.0	11.6 \pm 5.7
Negative symptoms	8.2 \pm 1.0	8.0 \pm 0.2	8.4 \pm 2.0	8.0 \pm 0.3	12.0 \pm 5.9	11.1 \pm 4.2
Disorganization	10.2 \pm 1.2	10.1 \pm 0.3	10.3 \pm 0.7	10.1 \pm 0.4	12.5 \pm 4.1	11.8 \pm 2.5
Excitement	8.3 \pm 1.1	8.3 \pm 0.5	8.6 \pm 1.4	8.3 \pm 0.6	9.7 \pm 2.7	9.7 \pm 2.5
Emotional distress	9.2 \pm 2.1	9.4 \pm 1.7	9.9 \pm 2.6	9.7 \pm 2.2	13.2 \pm 5.2	14.1 \pm 5.0
Remission (%)	–	–	–	–	57%	62%

PANSS, Positive and Negative Syndrome Scale; dis, disorder; NOS, not otherwise specified.

Means \pm s.d., range are reported.

^aRange: from –100 (entirely left-handed) to +100 (entirely right-handed).

^bRange: 0 = no education to 8 = university degree.

^cCumulative exposure, lifetime until baseline in haloperidol equivalents.

^dCumulative exposure, last 3 years in haloperidol equivalents.

^eHistory of major depressive disorder, no current episodes at baseline or in last 3 years.

^fMean number of times; lifetime.

^gMean number of times; last 12 months.

^hWeekly consumptions; lifetime.

ⁱWeekly consumptions; last 12 month.

($\chi^2 = 2.9$, $df = 2$, $p = 0.24$) (all analyses with linear environmental variables). The results did not change after stratification by number of scan directions (76 directions: cannabis exposure; lifetime: $\chi^2 = 1.4$, $df = 2$, $p = 0.49$, last year: $\chi^2 = 0.2$, $df = 2$, $p = 0.89$, childhood trauma exposure: $\chi^2 = 2.3$, $df = 2$, $p = 0.31$; and 81 directions: cannabis exposure; lifetime: $\chi^2 = 1.2$, $df = 2$, $p = 0.56$, last year: $\chi^2 = 1.5$, $df = 2$, $p = 0.48$, childhood trauma exposure: $\chi^2 = 0.2$, $df = 2$, $p = 0.93$).

Cross-sectional analysis of FA and environmental risk factors at follow-up

No significant associations between cannabis exposure (linear variable) and FA (lifetime: $B = 1.0 \times 10^{-4}$, $p = 0.95$, last year: $B = -3.0 \times 10^{-6}$, $p = 0.88$) or between childhood trauma exposure (linear variable) and FA ($B = -0.001$, $p = 0.67$) were found at follow-up.

Table 2. Within-group distribution of the environmental exposures

	Controls	m/f ratio	Siblings	m/f ratio	Patients	m/f ratio	χ^2	p
Cannabis use (baseline)								
No	58 (73%)	34/66	59 (64%)	47/53	31 (39%)	48/52	29.8	0.00
Moderate	8 (10%)	38/62	11 (12%)	36/64	6 (8%)	33/67		
Heavy	13 (17%)	46/54	22 (24%)	73/27	43 (53%)	84/16		
Cannabis use (follow-up)								
No	37 (76%)	38/62	35 (64%)	49/51	20 (39%)	60/40	17.6	0.001
Moderate	5 (10%)	40/60	6 (11%)	33/67	5 (10%)	20/80		
Heavy	7 (14%)	43/57	14 (25%)	71/29	26 (51%)	88/12		
Childhood trauma (baseline)								
Low	38 (48%)	47/53	36 (39%)	50/50	21 (25%)	48/52	20.1	0.00
Moderate	26 (32%)	27/73	34 (36%)	50/50	22 (26%)	82/18		
Heavy	16 (20%)	25/75	23 (25%)	61/39	41 (49%)	71/29		
Childhood trauma (follow-up)								
Low	21 (43%)	52/48	23 (42%)	52/48	17 (31%)	53/47	6.5	0.17
Moderate	18 (37%)	28/72	18 (33%)	59/41	15 (27%)	80/20		
Heavy	10 (20%)	30/70	14 (25%)	43/57	23 (42%)	83/17		

The number of subjects per group (and proportion of total group) for the baseline ($n = 258$) and longitudinal analysis (follow-up, $n = 159$) per environmental stress factor. The difference between groups in proportion of high, medium, and low cannabis use was analyzed with the Pearson's (χ^2). m/f ratio, male/female ratio.

Cannabis

No significant interaction was found between last year cannabis use and group in the model of FA ($\chi^2 = 0.8$, $df = 2$, $p = 0.66$). A significant interaction was found between, respectively, (lifetime) cannabis exposure ($\chi^2 = 9.3$, $df = 2$, $p = 0.01$) and group in the model of FA. This interaction remained significant after controlling for childhood trauma ($\chi^2 = 9.6$, $df = 2$, $p = 0.008$), BMI ($\chi^2 = 9.7$, $df = 2$, $p = 0.008$), alcohol use ($\chi^2 = 9.8$, $df = 2$, $p = 0.008$), and other drug use ($\chi^2 = 7.6$, $df = 2$, $p = 0.02$) (all linear variables).

Stratified analyses showed a mean FA decrease in the heavy cannabis using patients, which was significantly different from the controls and the siblings. An association in opposite direction was found in cannabis-using siblings, but only for the moderate cannabis exposure level and not for the highest exposure level (see Table 3).

Childhood trauma

A significant interaction between childhood trauma exposure and group in the model of FA ($\chi^2 = 6.1$, $df = 2$, $p = 0.05$) was found. The interaction remained significant after controlling for alcohol use ($\chi^2 = 8.8$, $df = 2$, $p = 0.01$), inconclusive for lifetime cannabis use ($\chi^2 = 4.9$, $df = 2$, $p = 0.09$) and BMI ($\chi^2 = 5.5$, $df = 2$, $p = 0.06$), however not significant anymore with addition of other drug use ($\chi^2 = 4.4$, $df = 2$, $p = 0.11$) (all linear variables).

Stratified analyses showed a mean FA decrease in patients exposed to a high childhood trauma level, which was significantly different from the siblings and inconclusive from the controls (see Table 3).

Longitudinal analysis of Δ FA and environmental risk factors

In the whole group, there was no significant association between, respectively, lifetime cannabis exposure ($B = -3.0 \times 10^{-5}$, $p = 0.16$), last year cannabis exposure ($B = -1.0 \times 10^{-5}$, $p = 0.45$), or childhood trauma exposure (all linear variables) and Δ FA ($B = -7.0 \times 10^{-4}$, $p = 0.13$).

Cannabis

There was a significant interaction between (lifetime) cannabis exposure and group in the model of Δ FA ($\chi^2 = 6.2$, $df = 2$, $p = 0.04$). This interaction remained significant after controlling for childhood trauma ($\chi^2 = 5.9$, $df = 2$, $p = 0.05$), BMI ($\chi^2 = 5.8$, $df = 2$, $p = 0.05$), alcohol use ($\chi^2 = 5.9$, $df = 2$, $p = 0.05$), other drug use ($\chi^2 = 7.4$, $df = 2$, $p = 0.02$), and scan type ($\chi^2 = 6.5$, $df = 2$, $p = 0.04$). After exclusion of the 26 participants with a history of depression (16% reduction in sample size), the interaction became inconclusive ($\chi^2 = 5.4$, $df = 2$, $p = 0.07$) (all linear variables).

Stratified analyses showed a significant effect in patients, indicating a decrease in FA over time with increasing cannabis exposure in patients, resulting in a significant group difference between patients and controls and between patients and siblings. Compared with patients with no cannabis use, patients with heavy cannabis consumption had significantly more FA decrease over time. This was not the case for the moderate v. no cannabis use comparison (Table 4, Fig. 1).

Childhood trauma

A significant interaction between trauma exposure and group in the model of Δ FA ($\chi^2 = 11.3$, $df = 2$, $p = 0.003$) was found. The interaction remained significant after controlling for lifetime cannabis

Table 3. Mean FA as a function of group status and environmental exposure at follow-up

Environmental exposure	Patients			Siblings			Controls			Group differences	
	N	B	p	N	B	p	N	B	p	χ^2	p
Lifetime cannabis											
Cannabis (linear)		−0.005	0.02*		0.004	0.07		0.003	0.31	P v. C	4.6
										P v. S	8.2
										S v. C	0.09
No cannabis use ^a	21			39			45				
Moderate cannabis use	5	−0.01	0.29	7	0.01	0.04*	4	0.002	0.84	P v. C	0.77
										P v. S	4.4
										S v. C	1.2
Heavy cannabis use	31	−0.01	0.02*	14	0.007	0.14	8	0.007	0.30	P v. C	4.8
										P v. S	7.2
										S v. C	0.007
Childhood trauma											
Trauma (linear)		−0.006	0.03*		0.002	0.52		0.003	0.33	P v. C	4.8
										P v. S	4.1
										S v. C	0.09
Low trauma ^a	18			28			30				
Medium trauma	24	−0.009	0.09	23	−0.005	0.31	19	0.005	0.26	P v. C	4.0
										P v. S	0.4
										S v. C	2.3
High trauma	18	−0.01	0.03*	10	0.007	0.24	9	0.004	0.53	P v. C	3.5
										P v. S	5.7
										S v. C	0.1

N, number of participants; P v. C, patients v. controls; P v. S, patients v. siblings; S v. C, siblings v. controls.

Results from the interaction: environmental exposure × group in the model of FA. The B's represent the stratified group effect sizes. Group differences are displayed with χ^2 , and the p value (<0.05*).

^aReference level.

use ($\chi^2 = 12.3$, $df = 2$, $p = 0.002$), BMI ($\chi^2 = 10.5$, $df = 2$, $p = 0.005$), alcohol use ($\chi^2 = 12.0$, $df = 2$, $p = 0.003$), other drug use ($\chi^2 = 14.6$, $df = 2$, $p = 0.0007$), and scan type ($\chi^2 = 11.5$, $df = 2$, $p = 0.003$). The interaction was inconclusive after exclusion of the 26 participants with a history of depression ($\chi^2 = 5.6$, $df = 2$, $p = 0.06$) (all linear variables).

Stratified analysis revealed a significant negative association between childhood trauma and Δ FA in patients, resulting in a significant patient–control and patient–sibling difference. Compared with low trauma exposure, patients exposed to high trauma levels had significantly more FA decrease over time. This was not the case for moderate compared with low trauma exposure (Table 4, Fig. 1).

Sensitivity analyses in AP medication subgroups

In the AP medication subgroup analyses (with smaller N), interactions between both environmental risk factors and group in the model of Δ FA remained largely significant, most prominent in patients with the lowest AP exposure levels (lifetime and 3-year interval). Wald tests showed that the significant negative

associations between the environmental factor and Δ FA in the low AP subgroups were significantly different for the patient–control and the patient–sibling comparison (see online Supplementary Table S1).

Discussion

Despite the absence of cross-sectional associations between environmental risk factors and WM FA at baseline, there were significant interactions between group and cannabis and childhood trauma exposure in models of FA at follow-up and FA change over a 3-year time period. Patients exposed to the highest levels of cannabis or childhood trauma had a greater FA decrease over time compared with controls and siblings.

Cannabis exposure and WM alterations

Higher levels of (lifetime) cannabis exposure in patients with psychotic disorder were not associated with FA alterations at baseline, but with significant FA reduction over a 3-year period compared with siblings and healthy controls. This is the first

Table 4. Mean Δ Fa as a function of group status and environmental exposure

Environmental exposure	Patients				Siblings				Controls				Group differences		
	<i>N</i>	Δ FA mean \pm s.d.	<i>B</i>	<i>p</i>	<i>N</i>	Δ FA mean \pm s.d.	<i>B</i>	<i>p</i>	<i>N</i>	Δ FA mean \pm s.d.	<i>B</i>	<i>p</i>	χ^2	<i>p</i>	
Lifetime cannabis															
Cannabis (linear)			−0.003	0.02*			0.001	0.41			0.001	0.39	P v. C	4.1	0.04*
													P v. S	4.7	0.03*
													S v. C	0.03	0.87
No cannabis use ^a	20	0.0014 \pm 0.03			35	−0.0040 \pm 0.03			37	−0.0005 \pm 0.03					
Moderate cannabis use	5	0.0038 \pm 0.03	0.002	0.60	6	0.0003 \pm 0.03	0.004	0.25	5	0.0040 \pm 0.03	0.003	0.47	P v. C	0.02	0.90
													P v. S	0.1	0.71
													S v. C	0.1	0.80
Heavy cannabis use	26	−0.0041 \pm 0.03	−0.006	0.02*	14	−0.0022 \pm 0.03	0.002	0.51	7	0.0040 \pm 0.03	0.002	0.47	P v. C	3.7	0.05*
													P v. S	4.3	0.04*
													S v. C	0.03	0.86
Childhood trauma															
Trauma (linear)			−0.004	0.0005*			0.0002	0.90			0.002	0.26	P v. C	9.7	0.002*
													P v. S	6.4	0.01*
													S v. C	0.6	0.45
Low trauma ^a	17	0.0034 \pm 0.03			23	−0.0018 \pm 0.03			21	−0.00003 \pm 0.03					
Medium trauma	15	0.0016 \pm 0.03	−0.002	0.42	18	−0.0068 \pm 0.03	−0.003	0.17	18	−0.00002 \pm 0.03	0.0008	0.75	P v. C	0.7	0.42
													P v. S	0.1	0.76
													S v. C	1.4	0.24
High trauma	23	−0.0060 \pm 0.03	−0.009	0.0005*	14	−0.0004 \pm 0.03	0.001	0.71	10	0.0031 \pm 0.03	0.004	0.23	P v. C	10.0	0.002*
													P v. S	7.2	0.007*
													S v. C	0.4	0.50

N, number of participants; P v. C, patients v. controls; P v. S, patients v. siblings; S v. C, siblings v. controls.

Results from the interaction: environmental exposure \times group in the model of Δ Fa. The *B*'s represent the stratified group effect sizes. Group differences are displayed with χ^2 , and the *p* value (<0.05*).

^aReference level.

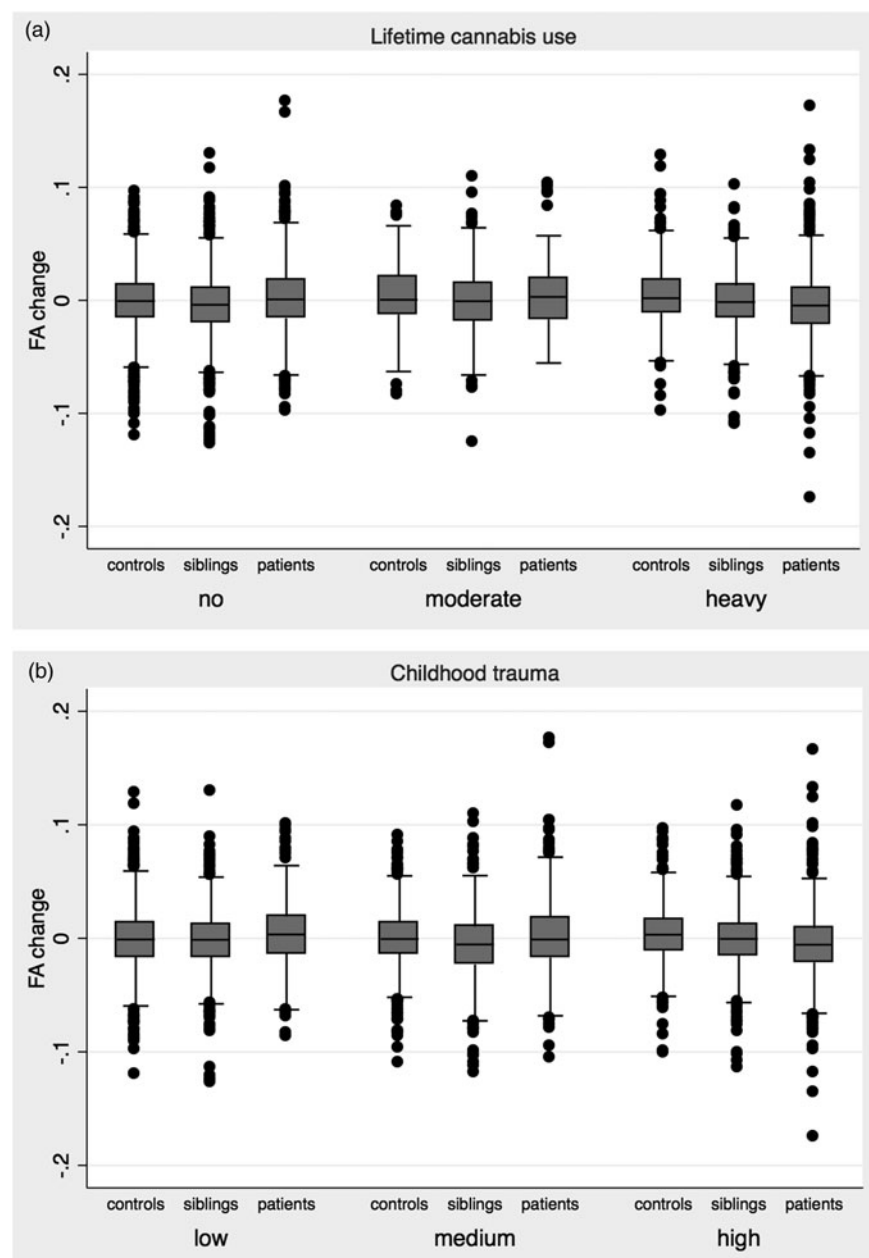


Fig. 1. The association between, respectively, cannabis (a) and childhood trauma (b) (dummy variables) and Δ FA, stratified per group. The effect of high cannabis exposure v. no cannabis exposure and high trauma exposure v. low trauma exposure on mean whole-brain Δ FA was significantly different for patients compared with controls (cannabis; $\chi^2 = 3.7$, $p = 0.05$, trauma; $\chi^2 = 10.0$, $p = 0.002$) and for patients compared with siblings (cannabis; $\chi^2 = 4.3$, $p = 0.04$, trauma; $\chi^2 = 7.2$, $p = 0.007$) (* $p < 0.05$).

longitudinal study examining the effect of cannabis on WM FA in relation to (familial risk for) psychotic disorder, suggesting that the extent of WM alterations is conditional on the level of cannabis exposure in patients with the disorder. Especially, cannabis use before or at disease onset may cause an additional reduction in WM FA, given the absence of an interaction between group and last year cannabis use in the model of Δ FA. This finding complies with other structural imaging findings of more severe WM deficits in young adults exposed to cannabis prior to the age of 16 (Cookey *et al.*, 2014). It strengthens the evidence, from both pre-clinical human and animal models, for a neurotoxic effect of cannabis in adolescence (Rubino and Parolaro, 2014); a sensitive age period for the neuronal maturation of the endocannabinoid system, possibly resulting in disrupted network connectivity of various brain areas.

To date, three longitudinal DTI studies examined substance abuse in non-psychotic populations. A lower rate of change in

FA was found in adolescent cannabis users ($n = 23$) in five clusters of fronto-parietal association fibers over a 2-year interval (Becker *et al.*, 2015). Moreover, a significant FA decrease over time in the left ILF in adolescents with cannabis use disorder ($n = 19$), associated with more cannabis exposure, compared with healthy controls (Epstein and Kumra, 2015). A third study showed poorer WM integrity after an 18-month follow-up, although mainly predicted by alcohol, not marijuana, in seven fronto-parietal tracts in adolescent substance users ($n = 41$) (Bava *et al.*, 2013).

In previous cross-sectional studies, positive as well as negative associations between FA and cannabis use in patients with schizophrenia have been reported. James *et al.* (2011) revealed associations between early cannabis use and decreased FA in, e.g. the internal capsule, corona radiata, superior and ILF, in patients with adolescent-onset schizophrenia (James *et al.*, 2011). In contrast, Peters *et al.* (2009) found FA increases in the bilateral uncinate fasciculus, anterior internal capsule, and frontal WM in

patients with recent-onset schizophrenia who had started using cannabis before the age of 17 years, compared with a similar group with no history of cannabis use (Peters *et al.*, 2009). Reduced FA has also been found in the splenium of the corpus callosum in non-cannabis using patients with schizophrenia compared with patients with schizophrenia and early-onset cannabis use (before age 15 years) (Dekker *et al.*, 2010). It has been shown that cannabis use may have different effects at various neurodevelopmental stages of life (Jakabek *et al.*, 2016). In the present study, absence of a significant cross-sectional association between FA and lifetime cannabis exposure at baseline in contrast to significant associations at follow-up between, respectively, high and moderate cannabis exposure and FA in patients and siblings compared with controls may imply an age-related effect. The effect of cannabis on brain WM may only be visible after many years, depending on the WM developmental curvature of the specific subject and the timing of the measurement.

The opposite direction of effect, i.e. the FA increases in relatives with increasing lifetime cannabis exposure may suggest a delayed maturation, an imaging artifact or even a protective effect of a small amount of cannabis. A cannabinoid neuroprotective effect on brain matter with improvement in WM efficiency (Westlye *et al.*, 2010) has been proposed by recent *in vitro* studies (Sarnecki and Mechoulam, 2005).

The negative association between especially the heavy cannabis using patients with psychotic disorder and FA may fit with the hypothesis that heavy cannabis use at a young age may have altered the normal trajectory of WM brain maturation. Interference on the extensive pruning and myelination processes in an already vulnerable adolescent brain (Lubman *et al.*, 2015) may have caused additional reduction in WM FA later on in life. Whether this has clinical implications or influences on long-term prognosis needs further investigation.

Childhood trauma exposure and WM alterations

The present study examined the association between childhood trauma and FA in individuals with (risk for) psychotic disorder. At baseline, neither a significant interaction between childhood trauma exposure and group in the model of FA was found, nor a main effect of childhood trauma in any of the groups. However, at follow-up, a significant (dose-response) negative association between childhood trauma exposure and group in the model of FA was found in patients with psychotic disorder. In other words, higher exposure to childhood trauma is associated with lower whole-brain mean FA later in life. As with cannabis, differences in baseline and follow-up results may be explained by the timing of genetic and environmental influences (and their interactions) impacting cerebral plasticity during the life span.

The follow-up findings are in line with several studies that show reduced FA in non-psychotic traumatized subjects (Choi *et al.*, 2012; Daniels *et al.*, 2013) in stress-processing-related areas, such as the corpus callosum (Jackowski *et al.*, 2008; Paul *et al.*, 2008) and the cingulum bundle (Wang *et al.*, 2010; Zhang *et al.*, 2011). Thus, cross-sectional studies indicate that the FA reductions in traumatized populations may show overlap with the WM abnormalities in schizophrenia (Kubicki *et al.*, 2007; Ellison-Wright and Bullmore, 2009), suggesting that (part of) the WM tract alterations may be non-specific, contributing to different phenotypes.

The current study did also find a greater FA decline over a 3-year period in the patients with the highest level of childhood trauma exposure with respect to siblings and healthy controls. This significant FA decline over time associated with higher levels of childhood trauma may fit with the literature describing the neurotoxic impact of childhood trauma on WM development at a sensitive age period (Heim and Binder, 2012).

The patient-specific finding with regard to childhood trauma may refer to a complicated interplay between trauma-related factors and psychosis-related factors to account for the more pronounced WM alterations, predominantly in the group with the highest trauma exposure. Although a causal relationship between childhood trauma and WM decreases cannot be determined from these data, experiencing severe childhood trauma may cause an additive effect on already disrupted WM development. Alternatively, illness-related factors such as disadvantageous life style and health issues (e.g. reduced physical activity, social deprivation, smoking) (von Hausswolff-Juhlin *et al.*, 2009) may have contributed to increased cerebral vulnerability in patients, either or not in interaction with the environmental exposures under investigation.

Methodological considerations

Apart from the strength of this study – a relatively large longitudinal imaging design with a gene-environment approach – some limitations need to be addressed.

The sample size of some longitudinal subgroup analyses was only modest or small, resulting in loss of power (and thus weak statistical effects) and increased likelihood of false-negative results. Taken together with a rather skewed gender distribution in our sample, gender-specific sub-analyses were not considered feasible although it is known that several WM tracts show gender-specific FA differences (Menzler *et al.*, 2011; Kanaan *et al.*, 2014).

A full understanding of the biological and clinical relevance of the reported small changes in FA is hampered. Nevertheless, one can imagine that disproportionally higher changes may arise due to stronger regional effects, either or not in combination with higher mean trauma levels. Future studies with larger sample sizes may provide more precise estimates of regional FA effect sizes associated with these environmental exposures.

Conform the various results across studies on the association between AP use and WM alterations (Szeszko *et al.*, 2008; Ozelik-Eroglu *et al.*, 2014; Reis Marques *et al.*, 2014), and the small effect of last 3-year and lifetime AP use on Δ FA found in our previous analyses (Domen *et al.*, 2017), the current results suggest a minor confounding effect of AP use as not all the G \times E interactions remained significant in different AP subgroups. However, the results of these sensitivity analyses must be viewed with caution given the sizable lack of power (patient-AP subgroups comprised one-third of the sample).

It is unlikely that the two DTI sequences used at baseline would have contributed to a systematic bias, as the proportions of the two sequences were almost equal between the groups. In addition, stratified analyses (by number of scan directions) and adjustment for scanning sequence did not change the results, fitting the suggestion that the variation in tensor estimation is negligible with more than 30 diffusion directions (Jones, 2004). Extracting mean FA values from the TBSS skeleton has the disadvantage of only examining the central portion of the WM tract, but will procure that WM was indeed examined. This is in line

with more recent cannabis – diffusion studies that took a distance from a voxel-based comparison approach (Jakabek *et al.*, 2016).

Lastly, FA is a rather non-specific diffusion measure, containing information on myelination, fiber organization, and number of axons, and therefore not completely synonymous to ‘WM integrity’, so that the current findings must be interpreted with caution (O’Donnell and Pasternak, 2015). Nonetheless, a whole-brain, hypothesis-generating approach was chosen, as studies investigating the influence of environmental risk factors on WM alterations in patients with psychotic disorder are scarce and ambiguous.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291718001320>

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Conflict of interest. Jim van Os is or has been, in the last 3 years, an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from Lundbeck and Janssen. Machteld Marcelis has received, in the last 3 years, financial compensation as an independent symposium speaker from Lundbeck and Janssen. All other authors report no biomedical financial interests or potential conflicts of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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